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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/420,433	10/12/1999	DAVID SIDRANSKY	JHU1180-1	2810

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EXAMINER	
JOHANNSEN, DIANA B	

ART UNIT	PAPER NUMBER
1634	19

DATE MAILED: 05/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/420,433	Applicant(s) SIDRANSKY, DAVID
	Examiner Diana Johannsen	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of species c), drawn to methods requiring detection of a mutant/neoplastic target nucleic acid in a surgical margin adjacent to an excised tumor in Paper No. 16 is acknowledged. However, upon further consideration, the restriction requirement set forth in paper no. 14 is withdrawn. Claims 1-27 have been examined.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 2-3 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-3 are indefinite over the recitation of the limitation "the mutant nucleic acid" in claim 2. While claim 1 recites a "mutant target nucleic acid," there is insufficient antecedent basis for the limitation "the mutant nucleic acid."

Claim 21 is indefinite over the recitation of the limitation "the mutant nucleic acid." While claim 20 recites a "mutant target nucleic acid," there is insufficient antecedent basis for the limitation "the mutant nucleic acid."

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 1-8, 10, 12, 14-16, and 18-19 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Nees et al (Cancer Research 53(18):4189-4196 [9/1993]).

Nees et al disclose methods for detecting p53 mutations in tumor, tumor-adjacent, and tumor-distant specimens from head and neck cancer patients (see entire reference). Nees et al's methods comprise steps of extracting nucleic acid from specimens and detecting p53 mutations present therein (see p. 4190). Nees et al disclose that tumor-adjacent and tumor distant specimens did not exhibit neoplastic morphology (see, e.g., p. 4189). The "tumor adjacent" specimens employed by Nees et al were obtained immediately after tumor removal (p. 4189), and constitute tumor margin specimens as well as tissues "from a surgical margin adjacent" to excised tumor. Nees et al disclose that mutated p53 nucleic acids were detected in such tumor adjacent samples (see, e.g., Table 3, p. 4191, 4193). With respect to claims 2-3, 12, and 14-16, it is noted that the amplification and ISH methods of Nees et al at p. 4190 meet the limitations of these claims. With respect to claims 5 and 15-16, it is noted that it is an inherent property of p53 that it is a tumor suppressor.

6. Claim 13 is rejected under 35 U.S.C. 102(a) as being clearly anticipated by Nees et al (Cancer Research 53(18):4189-4196 [9/1993]), in light of the teachings of Sobol et al (U.S. Patent No. 5,543,296 [8/6/1996; effective filing date 6/26/1991]).

Nees et al disclose methods for detecting p53 mutations in tumor, tumor-adjacent, and tumor-distant specimens from head and neck cancer patients (see entire

reference). Nees et al's methods comprise steps of extracting nucleic acid from specimens and detecting p53 mutations present therein (see p. 4190). Nees et al disclose that tumor-adjacent and tumor distant specimens did not exhibit neoplastic morphology (see, e.g., p. 4189). The "tumor adjacent" specimens employed by Nees et al were obtained immediately after tumor removal (p. 4189), and constitute tumor margin specimens as well as tissues "from a surgical margin adjacent" to excised tumor. Nees et al disclose that mutated p53 nucleic acids were detected in such tumor adjacent samples (see, e.g., Table 3, p. 4191, 4193). It is noted that Nees et al do not disclose the sensitivity of PCR in detecting "neoplastic" nucleic acids. However, Sobol et al disclose that PCR is sufficiently sensitive to detect a target nucleic acid present in only 1 of 10,000 cells (col 2, lines 46-52). Accordingly, given the disclosure of Sobol et al, it is noted that it is an inherent property of the method of Nees et al that it meets the requirement of claim 13, in that the method would detect "no more than an average of about one out of every ten thousand cells of said tissue" having a "neoplastic" nucleic acid.

Claim Rejections - 35 USC § 103

7. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nees et al (Cancer Research 53(18):4189-4196 [9/1993]) in view of Watling et al (Head and Neck 14;437-444 [11-12/1992]).

Nees et al disclose methods for detecting p53 mutations in tumor, tumor-adjacent, and tumor-distant specimens from head and neck cancer patients (see entire

reference). Nees et al's methods comprise steps of extracting nucleic acid from specimens and detecting p53 mutations present therein (see p. 4190). Nees et al disclose that tumor-adjacent and tumor distant specimens did not exhibit neoplastic morphology (see, e.g., p. 4189). The "tumor adjacent" specimens employed by Nees et al were obtained immediately after tumor removal (p. 4189), and constitute tumor margin specimens as well as tissues "from a surgical margin adjacent" to excised tumor. Nees et al disclose that mutated p53 nucleic acids were detected in such tumor adjacent samples (see, e.g., Table 3, p. 4191, 4193). Nees et al do not teach employing their method on specimens taken from margins surrounding a benign neoplasm. Watling et al disclose that p53 overexpression is detected in the majority of malignant head and neck tumors, whereas no such overexpression is detected in benign head and neck tumors (see entire reference, especially p. 439). Thus, the teachings of Watling et al establish that p53 expression differs in malignant head and neck tumors as compared to benign head and neck tumors. In view of the teachings of Watling et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Nees et al so as to have practiced Nees et al's methods of detecting p53 mutations on specimens obtained from benign head and tumors, as well as benign tumor-adjacent specimens. An ordinary artisan would have been motivated to have made such a modification in order to have determined whether the p53 mutations present in and adjacent to malignant neoplasms in head and neck cancer patients are present or absent in benign tumors

and/or tumor margins, for the advantage of establishing a rapid method for either detecting or differentiating benign and malignant neoplasms of the head and neck.

8. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nees et al (Cancer Research 53(18):4189-4196 [9/1993]) in view of Mullis et al (U.S. Patent No. 4,683,195 [7/28/1987]).

The teachings of Nees et al are set forth in paragraph 7, above. While Nees et al disclose the sequencing of PCR products (p. 4190), Nees et al do not do not teach a step of cloning amplified target sequences prior to detection. Mullis et al disclose that the cloning of amplification products allows one to rapidly sequence or express a target molecule of interest (see, e.g., col 15, line 16-col 16, line 13). In view of the teachings of Mullis et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nees et al so as to have cloned amplification products comprising mutated p53 sequences. An ordinary artisan would have been motivated to have made such a modification in order to have facilitated both the sequencing and expression of such products, for the advantages of convenience and efficiency in further analysis of mutated p53 sequences found in and adjacent to tumors. It is noted that one of ordinary skill in the art would have been motivated to have expressed such sequences in order to have, e.g., prepared antigenic fragments of mutated p53 gene products for use in antibody preparation and subsequent analysis of the expression of abnormal forms of p53 in and around tumors.

9. Claims 20-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nees et al (Cancer Research 53(18):4189-4196 [9/1993]) in view of Sobol et al (U.S. Patent No. 5,543,296 [8/6/1996; effective filing date 6/26/1991]).

The teachings of Nees et al are set forth in paragraph 7, above. While Nees et al disclose detecting mutated p53 sequences in a variety of tumor-distant specimens, Nees et al do not disclose detection of such sequences in lymph node tissue specimens lacking neoplastic pathology. Sobol et al teach methods for detecting carcinoma metastases comprising extraction of nucleic acids from a sample of tissue or fluid and detection of a "carcinoma associated sequence" (see entire reference). The samples analyzed by Sobol et al's methods may include both fluids and tissues, including lymph nodes (see, e.g., col 4, lines 52-59). Sobol et al teach that conventional diagnostic methods may fail to detect residual or metastatic disease, and disclose that their methods are more sensitive than conventional methods, including histological analysis, allowing for detection of carcinoma metastases not detectable by histological analyses (see, e.g., col 2, lines 13-52; col 4, lines 33-35; col 5, lines 28-35). In view of the teachings of Sobol et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nees et al so as to have detected metastases of head and neck cancer by detecting mutated p53 nucleic acids in lymph nodes not exhibiting "morphological characteristics indicative of neoplastic pathology," as required by the claims. Given the teachings of Sobol et al regarding the greater sensitivity of extraction and amplification of tumor-associated nucleic acids as compared to histological analysis, an ordinary artisan would have been

motivated to have made such a modification for the advantage of detecting the spread of head and neck cancer to lymph nodes with greater accuracy and sensitivity. With respect to claims 21-22 and 25, it is noted that the amplification and ISH methods of Nees et al at p. 4190 meet the limitations of these claims. With respect to claims 23 and 27, it is noted that it is an inherent property of p53 that it is a tumor suppressor. With respect to claim 26, Sobol et al disclose that PCR is sufficiently sensitive to detect a target nucleic acid present in only 1 of 10,000 cells (col 2, lines 46-52).

10. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nees et al (Cancer Research 53(18):4189-4196 [9/1993]) in view of Knudson (Archives of Otolaryngology – Head and Neck Surgery 119(7):735-7 [7/1993]).

The teachings of Nees et al are set forth in paragraph 7, above. While Nees et al disclose detecting p53 nucleic acids containing mutations in tumor margin tissue specimens, Nees et al do not disclose detecting oncogenes containing mutations in such specimens. Knudson teaches that head and neck tumors may also contain mutated oncogenes, such as mutated forms of *ras* (see entire reference). In view of the teachings of Knudson, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nees et al so as to have employed the method in detecting mutated oncogenes (such as mutated forms of *ras*) in tumor-adjacent tissue specimens from head and neck cancer patients. An ordinary artisan would have been motivated to have made such a modification in order to have determined the diagnostic value of detecting such sequences in head and

neck tumors, tumor margins, and tumor-distant specimens, for the advantage of establishing rapid methods of detecting residual or metastatic disease.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,025,127. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. The instant claims are drawn to methods for detecting metastases, "neoplastic" nucleic acids, and nucleic acids that contribute "to the etiology of a neoplasm". Instant claims 1-11 and 18-24 require steps of extracting nucleic acid from a tumor margin (claims 1-11, 19) or lymph node (claims 20-24) and/or a tissue specimen "external to a primary neoplasm" (claim 18-24), and detecting target nucleic acid. Instant claims 12-17 and 25-27 require steps of isolating tissue from a surgical margin (claims 12-17) or lymph node (claims 25-27) and detecting

hybridization of a probe to said tissue. The instant claims encompass methods in which nucleic acids are amplified and detected (see, e.g., instant claims 2-3, 21). The '127 claims are drawn to methods for detecting mutated target nucleic acids and methods "for detecting the presence of a mammalian target nucleic acid which contributes to the etiology of a neoplasm". The '127 claims require steps of amplifying target nucleic acids with oligonucleotides that hybridize thereto. The '127 claims set forth target tissue types that include tumor margins and lymph nodes. The instant claims differ from the '127 claim in that the broadest of the instant claims do not require amplification, and in that the instant claims do not require the use of particular oligonucleotides in detection. However, the instant claims are sufficiently broad so as to encompass the '127 claims, and it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the '127 claims so as to have eliminated some of the limitations of the '127 claims (e.g., the requirement for particular oligonucleotides) so as to have arrived at the instant claims. An ordinary artisan would have been motivated to have made such a modification for the advantage of, e.g., increasing the number of different tumor types that could be detected by the claimed method. Accordingly, the instant claims and the '127 claims are not patentably distinct from each other.

It is noted that the Remarks of the Preliminary Amendment of paper no. 13 state that while the rejection of claims 1-18 over claims 1-4 of the '127 patent is traversed, "Applicant respectfully defers responding to the rejection until an indication is received that one or more claims are in condition for allowance."

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
May 4, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600